Kindly amend the above-identified patent application, without prejudice, as follows:

In the Claims

A1

4. (Amended) A method according to claim 3 wherein Q_1 and Q_2 are selected from substituted and unsubstituted phenyl.

Sub B3 #2

18. (Amended) In a method for treating cancer or other proliferative disorder comprising administering an effective amount of at least one mitotic phase cell cycle inhibitor or topoisomerase inhibitor to an animal in need of such treatment, the improvement comprising administering to said animal prior to administration of said mitotic phase cell cycle inhibitor or topoisomerase inhibitor an effective amount at least one cytoprotective α,β unsaturated aryl sulfone compound.

Remarks

Claims 1-22 are pending in the application. Claims 8-11 have been withdrawn from consideration.

Claims 4 has been amended to correct the inadvertent insertion of the word "compound" and to conform all the claims in the application to recite methods. Claim 18 has been amended to more particularly point out and define the invention. Marked-up versions of the amended claims are contained in Appendix A.

Response to Rejection under 35 U.S.C. § 112, para. 1

The Office Action rejects claims 12-22 under this provision because it is asserted that the specification does not reasonably provide enablement for "treating cancer".

To state a prima facie case for lack of enablement, the MPEP at §2164.04 places the burden on the examiner to provide a rational basis as to why the disclosure does not teach the manner and process of making and using the claimed invention to one of ordinary skill in the relevant art without undue

experimentation. (*See* IN RE WRIGHT, 999 F.2d 1557, 27 USPQ 2d 1510, 1513 (Fed. Cir.)).

The rational basis for this rejection constitutes the statements that "the treatment of all cancers broadly is unpredictable" and that "one of ordinary skill in the art would not believe that one compound could treat all types of cancer with a single therapeutic agent" (page 3, para. 2). These statements communicate nothing of the specific teachings in the present disclosure regarding the manner and method of making and using the present invention. Indeed, their very use as the rational basis for this rejection reveals a fundamental misunderstanding of the present invention.

Indeed, claims 12-17 do not recite a method for treating cancer. These claims ultimately depend from claim 1, which recites a method for protecting an animal from cytotoxic side effects associated with the administration of two classes of chemotherapeutic agent, namely, mitotic cell cycle inhibitors and topoisomerase inhibitors. Claims 12-17 recite differing method embodiments of claim 1, which vary as to the cytoprotective compound administered, the lead time for the administration of the cytoprotective compound or the mitotic phase cell cycle inhibitor administered. Thus, the rejection is improper as it relates to claims 12-17.

With respect to claims 18-22, applicants have amended claim 18 to more particularly point out and define the invention as an improvement in a method for treating cancer or other proliferative disorder. The improvement comprises administration of an effective amount of a cytoprotective α,β unsaturated aryl sulfone compound to protect the subject from the toxic effects of mitotic cell cycle inhibitors and topoisomerase inhibitors when used as antiproliferative agents. As amended, claim 18 does not recite a method for "treating cancer in general", but an improvement in a cancer treatment wherein a cytoprotective α,β unsaturated aryl sulfone is administered as an adjunct to cancer chemotherapy. Claims 19 through 22 recite differing method embodiments of claim 18, which vary as to the lag time of the administration of the inhibitor, the lead time of the administration of the cytoprotective compound and the

cytoprotective compound administered.

As described in the specification, the present invention aims to administer certain α,β unsaturated aryl sulfone compounds for "reducing or eliminating adverse effects of anticancer treatment with mitotic phase cell cycle inhibitors and topoisomerase inhibitors" (pg.12, line 31 to page 15, line 2; pg. 14, lines 3-12.) The *claimed* invention is not a cancer treatment, but rather an adjunct to such a treatment. Examiner's criticisms regarding the alleged unpredictability of cancer treatment generally, and whether a particular anticancer agent can be used to treat a broad range of different cancers, are therefore misplaced. Applicants do not claim a treatment of "all cancers", or even treatment of one cancer for that matter. Rather, applicants claim a method of cytoprotection of normal cells in a host subjected to cancer chemotherapy with two specific classes of chemotherapeutic agents, namely, mitotic cell cycle inhibitors and topoisomerase inhibitors. Examiner has not provide evidence or cogent reasoning why the invention *as claimed* is not enabled by the specification.

The specification provides ample support and description for the compounds used as cytoprotective agents, and the anticancer/antiproliferative agents which benefit from the toxicity-reducing adjunct therapy. The specification discloses that mitotic phase cell cycle inhibitors are chemical agents that inhibit "a cell's passage through any portion of the mitotic (M) phase of the cell cycle" (pg. 13, lines 22-24). These include taxanes, such as paclitaxel, vinca alkaloids, such as vincristine and vinblastine and several other compounds (pg. 13, lines 25-29). Moreover, the specification explains that paclitaxel is used as an initial treatment for ovarian, breast and lung cancer and that vincristine is a well-established, anti-mitotic drug for the treatment of breast cancer, Hodgkin's lymphoma and childhood cancers (pg. 13, line 30 to pg. 14, line 2).

Regarding topoisomerase inhibitors, the specification discloses that these are "chemical agents whose mechanism of action includes interfering with the function of a topoisomerase", which is an enzyme that "catalyzes the conversion of DNA from one topological form to another by introducing transient breaks in one or both strands of a DNA duplex" (pg. 14, lines 3-12). There are two kinds of

topoisomerase inhibitors: Type I includes, for example, adriamycin and etoposide; Type II includes, for example, camptothecin, irinotecan and topotecan (pg. 14, lines 13-15).

The examiner's action implies the claimed invention is the administration of α, β unsaturated aryl sulfones **as the cancer treatment.** This is not the claimed invention even though α, β unsaturated aryl sulfones are toxic to tumor cells. The recited invention comprises methods of administering α, β unsaturated aryl sulfones as cytoprotective agents to protect nontumor cells. The tumor cells are being treated by a separate and specific cytotoxic anticancer drug, which is either a mitotic phase cell cycle inhibitor or a topoisomerase inhibitor.

Thus, the present invention is directed to the dual administration of

(A) an agent which is either a mitotic phase cell cycle inhibitor or a topoisomerase inhibitor, and

(B) an agent which is a cytoprotector, having the form of an α, β unsaturated aryl sulfone compound,

in a specific sequence of administration. The specification discusses with precision, clarity and detail, the (A) agents, the (B) agents, and the cancers to be treated by the (A) agents. The rationale basis of the examiner's action falls wholly short of explaining why the disclosure does not teach the manner and method of the invention; for that reason, the examiner's action does not state a prima facie case for lack of enablement. Applicants request this rejection be withdrawn.

Response to Rejection under 35 U.S.C. 112, para. 2

The Office Action rejects claims 4-7 under this provision because it is asserted there is insufficient antecedent basis for the limitation of "a compound according to claim 3". The amendment to Claim 4 provides sufficient antecedent basis for the limitation of interest in claims 4 through 7.

Response to Rejection under 35 U.S.C. §102

The examiner's action rejects claims 1-7 as being anticipated by Reddy et

al. WO 99/18608. The action avers that Reddy et al. disclose a compound of formulas I, II, and III (as recited in claims 2 and 3), which is used in a method of treating breast and prostate tumor cells and which induces apoptosis of such tumor cells while sparing normal cells.

To anticipate a claim, a single reference must teach either expressly or inherently all of the recited elements of the claim, arranged as in the claim (MPEP §2131. *See* HYBRITECH V. MONOCLONAL ANTIBODIES, INC., 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986); RICHARDSON V. SUZUKI MOTOR CO., 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 120 (Fed. Cir. 1989). Essentially, the reference needs to "sufficiently describe the claimed invention to have placed the public in possession of it". MINNESOTA MINING & MFG. CO. V. JOHNSON & JOHNSON ORTHOPAEDICS, INC., 976 F.2d 1559, 1572, 24 U.S.P.Q.2d 1321, 1332 (Fed. Cir. 1992).

Claim 1 recites a method for protecting an animal from cytotoxic side effects of the administration of a mitotic phase cell cycle inhibitor or a topoisomerase inhibitor comprising administering to the animal, in advance of administration of said inhibitor, an effective amount of at least one cytoprotective α, β unsaturated aryl sulfone compound. Claims 2-7 ultimately depend from claim 1 and recite differing methods for protecting from cytotoxic side effects which vary as to the formulae of the administered cytoprotective compounds.

Reddy et al. teach styryl sulfone compounds having formulas I, II, III and IV (Reddy et al., pp: 3-5) as well as methods of treatment for cancer, particularly breast or prostate cancer, comprising administering a compound having formula II or III; methods of inhibiting growth of tumor cells, particularly breast or prostate tumor cells, by administering a compound having formula III; and methods of inducing apoptosis of tumor cells, particularly breast or prostate tumor cells, comprising administering a compound having formula III (Reddy et al, pp:2-5).

The Reddy et al. disclosure does not teach all of the recited claim elements. In particular, the recited claim elements of administering an α, β unsaturated aryl sulfone as a cytoprotector in advance of administering a mitotic cell phase inhibitor or topoisomerase inhibitor are absent. Indeed, on page 5,

para. 3, the Office Action admits this very fact. The Office Action states that "Reddy et al. WO99/18608 does not teach a method comprising the administration of compounds of formula I and II and III prior to the administration of a mitotic phase cell cycle inhibitor or a topoisomerase inhibitor." Inasmuch as the claims recite a method comprising elements which the Office Action admits are not taught by the purportedly-anticipating reference, the § 102 rejection fails. Applicants request its withdrawal.

Response to Rejection under 35 U.S.C. §103(a)

Claims 12-22 stand rejected as allegedly obvious over Reddy et al. and Griggs (Embase Abstract AN 1998287056). A prima facie obviousness rejection must adhere to the following tenets of patent law as set forth in the MPEP §2141, citing HODOSH V. BLOCK DRUG CO., INC., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986):

- The claimed invention must be considered as a whole. The combination of references must teach or suggest all the claim elements (*see also* IN RE WILSON, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970);
- The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination. That is, the art relied upon must contain some suggestion that would motivate the artisan to combine the references. (*See* IN RE FINE, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); IN RE SKINNER, 2 USPQ2d 1788, 1790 (Bd. Pat. App. & Int. 1986));
- The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. (*See* IN RE AMGEN, INC. V. CHUGAI PHARM. CO., 927 F.2d 1200, 1209, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991)).

Reddy et al. teach administration of certain styryl sulfone compounds to selectively inhibit tumor cell proliferation, particularly breast and prostate tumor cell proliferation. Griggs teaches the use of amifostine as a cytoprotective agent against myelotoxicity, nephrotoxicity, neurotoxicity in patients treated with ankylating and platinum agents, paclitaxel and radiation therapy. Combining these references teaches the following proposed modification: the use of

amifostine as a cytoprotective agent and the administration of styryl sulfone compounds as cytotoxic agents.

This proposed modification does not include all the elements of the claimed invention. Absent from the combination of Reddy et al. and Griggs are the following claimed elements:

(1) the administration of an effective amount of at least one **cytoprotective α, β unsaturated aryl sulfone compound**

(2) **before**

(3) the administration of a **mitotic phase cell cycle inhibitor or topoisomerase inhibitor.**

Thus, the combination of references does not teach or suggest all of the claimed elements, as required by the MPEP and patent law.

Moreover, citing a reference that discloses amifostine as a cytoprotectant indicates clearly that the rejection is not based on considering the claimed invention as a whole, as required by the MPEP and patent law. The specification reveals that the present invention aims to reduce the cytotoxic effects of mitotic phase cell cycle inhibitors or topoisomerase inhibitors in an animal by administration of specific cytoprotective compounds, α, β unsaturated aryl sulfone compounds. Amifostine cited by Griggs as a cytoprotectant does not have the structure or functionality of α,β unsaturated aryl sulfone compounds. As the specification states α, β unsaturated aryl sulfone compounds differ from other known cytoprotective agents in that they not only protect normal cells, but are also operationally cytotoxic in tumor cells (pg. 14, lines 16-18). However, "simultaneous exposure α, β unsaturated aryl sulfones and the inhibitor does not result in cytoprotection" (pg. 15, lines 6-7). Observations show, however, that first exposure to α, β unsaturated aryl sulfones results in normal cells entering transitory cycling arrest, a quiescent state, which allows them to remain unharmed by the later-administered growth inhibitors, the action of which cause tumor cell death as tumor cells continue cycling (spec., pg. 15, lines 8-15). Because of the specific functionality of α, β unsaturated aryl sulfones in protecting normal cells, administering amifostine is not at all an equivalent

element. Consequently, the Office Action, in combining these references to propound a proposed, obvious modification, has not considered the claimed invention as a whole.

Nor does the Office properly consider the teachings of Reddy et al. and Griggs as a whole as required by the MPEP and patent law. When they are so considered, it is clear that the impetus for putting these references together does not come from the reference teachings themselves, but from the examiner's selective choice of individual elements so as to arrive at a proposed modification tailored to appear substantially similar to the claimed invention. Because the desirability of putting together the references is not suggested from within the combination, impermissible hindsight has been used to pluck elements from the references without consideration for the context from which the elements were taken.

In particular, Reddy et al. do not teach administering α, β unsaturated aryl sulfones, or any compound as a cytoprotective agent; nor do they teach a method of administering a cytoprotective agent before administering either a mitotic phase cell cycle inhibitor or topoisomerase inhibitor. Importantly, Reddy et al. teach using certain α, β unsaturated aryl sulfone compounds as anticancer agents per se. (Reddy et al., pg, 7, line 26 to pg. 8, line 2).

To the point, Examples 28 and 29 discuss the effect of certain styryl sulfone compounds on the growth rates of four lines of cells, 1 normal and 3 tumor lines. (Reddy et al., pp:20-26). Examples 30 and 31 discuss the effect of a specific styryl sulfone on cell cycle regulation and the MPK pathway (Reddy et al., pp:26-29). The parameter of interest in these examples is the percentage of viable tumor cells compared with the percentage of viable normal cells after various time intervals. Thus, these examples provide a demonstration of the efficacy of the styryl sulfone compounds **as cytotoxic agents against tumor cells**. Reddy et al. teach nothing about the use of styryl sulfone compounds to protect normal cells against the toxicity of other anticancer agents.

It is only the Griggs reference that discloses a cytoprotective agent, specifically the compound amifostine. Amifostine is known chemically as

ethanethiol, 2-[(3-aminopropyl)amino]-, dihydrogen phosphate (ester) and has the following structural formula: $H_2N(CH_2)_3NH(CH_2)_2S\text{-}PO_3H_2$. As can be readily appreciated, this compound is not an α, β unsaturated aryl sulfone compound; nor does it bear any structural resemblance to an α, β unsaturated aryl sulfone. Accordingly, Griggs teaches nothing about the use of α, β unsaturated aryl sulfone compounds as cytoprotective agents. Further, there is no mention in Griggs as to the timing of the administration of the cytoprotective agent. Griggs does not disclose or suggest the recited feature that the cytoprotective agent is administered **before** the cytotoxic agent. Griggs therefore teaches nothing about the claimed invention of administering a cytoprotective α, β unsaturated aryl sulfone to a patient before a mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

In looking at the teachings of the cited references, it can be seen that the obviousness rejection does not follow the required tenets of patent law as demanded by the MPEP. The combination of Reddy et al. and Griggs does not teach all of the claim elements. When considered as whole, the Reddy et al./Griggs combination does not itself suggest proposed modifications that lead to the claimed invention. Consequently, the proposed modifications suggested by combining individual elements of Reddy et al. and Griggs arise from permissible hindsight obtained from the claimed invention itself. Applicants request this rejection be withdrawn.

Conclusion

The claims recite novel methods which advance the state of the art in a nonobvious manner. Reconsideration and allowance of the application is earnestly solicited. Rejoinder of withdrawn claims 8-11 is also requested, as claims generic to these dependent claims are now clearly allowable.

Respectfully submitted,

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APPENDIX A

As required by 37 C.F.R. 1.21(c) (ii), provided hereinbelow is a marked-up version of claims 4 and 18.

4. (Amended) A [compound] method according to claim 3 wherein Q_1 and Q_2 are selected from substituted and unsubstituted phenyl.

18. (Amended) In a [A] method for treating cancer or other proliferative disorder comprising administering an effective amount of at least one mitotic phase cell cycle inhibitor or topoisomerase inhibitor to an animal in need of such treatment, the improvement comprising administering to said animal prior to administration of said mitotic phase cell cycle inhibitor or topoisomerase inhibitor [to an animal] an effective amount at least one cytoprotective α,β unsaturated aryl sulfone compound [followed by an effective amount of at least one mitotic phase cell cycle inhibitor or topoisomerase inhibitor after administration of the cytoprotective α,β unsaturated aryl sulfone compound].